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Breastfeeding initiation or duration and longitudinal patterns of infections up to 2 years and skin rash and respiratory symptoms up to 8 years in the EDEN mother–child cohort

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1 **Title**

2 Breastfeeding initiation or duration and longitudinal patterns of infections up to 2 years, skin
3 rash and respiratory symptoms up to 8 years in the EDEN mother–child cohort

4 **Running head**

5 Breast milk and infections or respiratory symptoms

6 **Key words:**

7 Breastfeeding, infection, skin rash, wheezing, longitudinal pattern, birth cohort

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29 **Ethic Statement**

30 The EDEN mother-child cohort was approved by the Ethics Committee of the University

31 Hospital of Kremlin-Bicêtre on December 12, 2002, and data files were declared to the

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40 **Availability of data and materials**

41 The data underlying the findings cannot be made freely available because of ethical and legal

42 restrictions because the present study includes an important number of variables that,

43 together, could be used to re-identify the participants based on a few key characteristics and
44 then be used to access other personal data. Therefore, the French ethical authority strictly
45 forbids making such data freely available. However, they can be obtained upon request from
46 the EDEN principal investigator. Readers may contact barbara.heude@inserm.fr to request
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61 **Abstract**

62 This paper aimed to examine the effect of breastfeeding on longitudinal patterns of common
63 infections up to 2 years and respiratory symptoms up to 8 years. To assess the incidence and
64 reoccurrence of infections and allergic symptoms in the first years of life among 1,603
65 children from the EDEN mother-child cohort, distinct longitudinal patterns of infectious
66 diseases as well as skin rash and respiratory symptoms were identified by group-based
67 trajectory modeling (GBTM). To characterize infections, we considered the parent-reported
68 number of cold/nasopharyngitis and diarrhea from birth to 12 months and otitis and
69 bronchitis/bronchiolitis from birth to 2 years. To characterize allergy-related symptoms, we
70 considered the parent-reported occurrence of wheezing and skin rash from 8 months to 8
71 years and asthma from 2 years to 8 years. Then, associations between breastfeeding and these
72 longitudinal patterns were assessed through adjusted multinomial logistic regression.
73 Compared to never-breastfed infants, ever-breastfed infants were at lower risk of diarrhea
74 events in early infancy as well as infrequent events of bronchitis/bronchiolitis throughout
75 infancy. Only predominant breastfeeding duration was related to frequent events of
76 bronchitis/bronchiolitis and infrequent events of otitis. We found no significant protective
77 effect of breastfeeding on longitudinal patterns of cold/nasopharyngitis, skin rash or
78 respiratory symptoms. For an infant population with a short breastfeeding duration, on
79 average, our study confirmed a protective effect of breastfeeding on diarrhea events in early
80 infancy, infrequent bronchitis/bronchiolitis and, to a lesser extent, infrequent otitis events up
81 to 2 years but not on other infections, skin rash or respiratory symptoms.

82 **Introduction**

83 The World Health Organization (WHO) recommends exclusive breastfeeding in the first 6
84 months of life or at least the first 4 months of life (World Health Organization, 2003). At
85 birth, because of the small in utero exposure to antigens, the newborn's immune system is
86 immature. Human breast milk contains biologically active substances such as lactoferrin,
87 oligosaccharides or maternal leukocytes, which are thought to protect the infant against
88 infections but also promote the immune system's maturation (Field, 2006; Hanson et al.,
89 2003).

90 A recent review emphasized a protective effect of breastfeeding on diarrhea and respiratory
91 infections (Victora et al., 2016), with an estimated prevention of 72% of hospitalizations for
92 diarrhea and 57% of respiratory infections related to breastfeeding as well as a protective
93 effect on otitis media in children up to 2 years of age. Studies assessing effect of
94 breastfeeding on otitis media were mostly from high-income countries, and those assessing
95 effect of breastfeeding on diarrhea and respiratory infections were mostly from low- and
96 middle-income countries (Bowatte et al., 2015; Horta & Victora, 2013). Concerning allergic
97 disorders, a recent review concluded a protective effect of breastfeeding on asthma, but the
98 evidence was weaker for eczema and allergic rhinitis (Lodge et al., 2015). In this review, the
99 protective effect of breastfeeding on allergic disorders was greater in low- than high-income
100 countries.

101 In high-income countries, the preventive effect of breastfeeding on respiratory tract infections
102 and allergies is less consistent across studies (Bion et al., 2016; Bowatte et al., 2015; Chiu et
103 al., 2016; Lodge et al., 2015). In a cluster-randomized trial on promotion of breastfeeding
104 (PROBIT), breastfeeding was related to a reduced risk of gastrointestinal infections and
105 atopic eczema in the first year of life (Kramer et al., 2001). However, most studies have

106 reported infections and allergy-related diseases as outcomes at a specific time point but not
107 their longitudinal pattern throughout infancy and childhood. Assessing association of
108 breastfeeding with a more longitudinal approach could allow for new insights into the timing
109 and duration of the protective effect of breastfeeding on these outcomes.

110 In this context, the aim of this study was to examine the association between breastfeeding
111 and the trajectories of infections up to 2 years and skin rash or respiratory symptoms up to 8
112 years.

113 **Methods**

114 ***Study population***

115 The EDEN mother–child study is a prospective cohort designed to assess prenatal and
116 postnatal determinants of child growth, development and health (Heude et al., 2016). In brief,
117 2,002 pregnant women were recruited in two French university hospitals, before 24 weeks of
118 amenorrhea. Exclusion criteria were multiple pregnancies, known diabetes before pregnancy,
119 illiteracy and planning to move outside the region in the next 3 years. Written consent was
120 obtained from both parents.

121 ***Breastfeeding***

122 Information on breastfeeding was collected by questionnaires given to parents during the
123 maternity stay and at age 4, 8, and 12 months and 2 years of the child. The calculation of
124 breastfeeding duration was previously described in detail (Betoko et al., 2013). For the
125 present analysis, breastfeeding was defined as any breastfeeding when the infant received
126 breast milk and as predominant breastfeeding when the only milk received by the infant was
127 breast milk. Both breastfeeding definitions were assessed through their initiation (never vs
128 ever) and duration. The latter one was assessed as a continuous variable but, as the mean
129 duration of breastfeeding is very short in France (Wagner et al., 2015) and in order to avoid

130 confusion related to the term “long breastfeeding duration”, breastfeeding duration was also
131 assessed as a categorical variable (< 1 month, 1 to < 4 months, \geq 4 months).

132 ***Infections, skin rash and respiratory symptoms***

133 Data on infections, skin rash and respiratory symptoms were collected by questionnaires
134 completed by parents at age 4, 8 and 12 months of the child and then age 2, 3, 4, 5 and 8
135 years.

136 For infection-related outcomes, parents could report cold/nasopharyngitis (at age 4, 8 and 12
137 months), diarrhea (at age 4, 8 and 12 months), otitis (at age 4, 8 and 12 months, 2 years) and
138 bronchitis/bronchiolitis (at age 4, 8 and 12 months, 2 years). For skin rash and respiratory
139 symptoms, parents could report skin rash (at age 8 and 12 months, 2, 3, 4, 5 and 8 years),
140 wheezing (at age 8 and 12 months, 2, 3, 4, 5 and 8 years), and asthma (at age 2, 3, 4, 5 and 8
141 years). At each of these ages, parents were asked to report whether the event had occurred
142 since the last follow-up and for infections, the number of episodes (1, 2, \geq 3) during the
143 considered period.

144 ***Potential confounders***

145 Family history of allergy is a known risk factor for allergy development (Lack, 2008).
146 Because this family susceptibility results from an inappropriate reaction of the immune
147 system, it is also an important factor to consider when assessing infections in infancy.
148 Parental and sibling history of asthma, eczema, allergic rhinitis and food allergy were
149 collected during a face-to-face interview at 24 to 28 weeks of gestation. Infants were
150 considered at risk of allergy if at least one parent or sibling had one of these allergic
151 symptoms.

152 During the same interview, data on the study center, maternal education level, family monthly
153 income and smoking status were collected. Parity, sex, gestational age, delivery mode and
154 maternal age were collected at birth from obstetric and pediatric records. The main type of

155 childcare, age at first attendance at a collective care arrangement in the first year and age at
156 first introduction of solid food were collected from self-administered questionnaires at age 4,
157 8 and 12 months of the child.

158 *Study samples*

159 Children with missing data on birth weight were excluded from the analyses because they
160 represented early lost to follow-up (n = 103). Because analyses were run separately for
161 infections and skin rash or respiratory symptoms, children with data at only one time point or
162 less regarding any outcome were excluded (n = 232 for infections, n= 465 for skin rash and
163 respiratory symptoms). Children with missing data on any breastfeeding were excluded (n =
164 1). Finally, we excluded all children with missing data on potential confounding variables (n
165 = 63 for infections, n = 56 for skin rash and respiratory symptoms). Thus, our sample
166 consisted of 1,603 children for the analysis of infections and 1,377 for the analysis of skin
167 rash and respiratory symptoms.

168 *Statistical analyses*

169 Mothers included in the current analysis of infections were compared to their EDEN
170 counterparts by Student *t* test and chi-square test for continuous and categorical data,
171 respectively.

172 Among children with at least 2 documented time points for the considered outcome, available
173 data for the considered outcome at each time point were used to model the longitudinal
174 patterns, by Nagin's method for group-based trajectory modeling (D. Nagin, 2005). The
175 method is based on the underlying hypothesis that within a population, there are inherent
176 groups that evolve according to different patterns. The groups are not directly identifiable or
177 pre-established by sets of characteristics but are statistically determined by each series of
178 responses. Using the TRAJ procedure from SAS software, multiple models were created,
179 varying in number of groups and shapes (computed by polynomial equations). Age in months

180 at each time point was the independent variable. For infection patterns, we modeled the
181 number of episodes (none, 1, 2, ≥ 3) during each period (CNORM model). For skin rash and
182 respiratory symptom patterns, we modeled the occurrence of at least one event during each
183 period (LOGIT model). To choose the most suitable model for each outcome, we used 4
184 decision criteria (**Supplementary tables 2 and 3**). A more complex model (B) has been
185 preferred over a simpler model (A) only in case of higher Bayesian Information Criteria
186 (BIC), defined as follows: $2*(BIC_{modelB}-BIC_{modelA})>10$. Then, to identify the shape of patterns,
187 we considered the Average Posterior Probability (Average PP) (≥ 0.7), the difference between
188 the actual and the estimated prevalence (closest to 0) and the Odds of Correct Classification
189 (OCC) (> 5). As suggested by Nagin and Odgers (D. S. Nagin & Odgers, 2010), we also
190 systematically verified that selected models were plausible in real-life and therefore easily
191 explainable.

192 Bivariate analyses between breastfeeding initiation or duration (in 3 categories), whatever the
193 definition used, and longitudinal patterns of health outcomes involved chi-square tests and are
194 presented in **Supplementary tables 4 to 7**

195 The potential links between breastfeeding and longitudinal patterns of health outcomes were
196 assessed using multinomial logistic regression analyses. Analyses were run separately for
197 each definition of breastfeeding and each outcome. All multivariate analyses were adjusted
198 for potential confounding factors, previously identified in literature: family history of allergy
199 (at risk of allergy vs not-at-risk), parity (multiparous vs primiparous), sex (boys vs girls),
200 preterm birth, C-section delivery, age at first attendance at a collective care arrangement (< 4
201 months, 4 to < 8 months, 8 to 12 months, never attended within the 1st year), age at
202 introduction of solid food (< 4 months, 4 to < 6 months, ≥ 6 months), study center (Nancy vs
203 Poitiers), maternal smoking during pregnancy, maternal education level (secondary school or
204 less, high school, 2-year university degree, 5-year university degree), maternal age at birth ($<$

205 25 years, 25 to 29 years, 30 to 34 years, > 34 years) and monthly family income (\leq €1,500,
206 €1,501 to €2,300, €2,301 to €3,000, €3,001 to €3,800, \geq €3,801).

207 As no interaction was highlighted between family history of allergies and breastfeeding (all p-
208 value \geq 0.5), analyses were not stratified on family history of allergies.

209 $P < 0.05$ was considered statistically significant. All analyses were carried out using SAS
210 version 9.4 (SAS, Cary, NC).

211 **Results**

212 The mothers included in our analyses of infections were compared with their non-included
213 counterparts (**Supplementary table 1**). Briefly, non-included mothers were younger, with
214 lower education level, lower family income and initiate less breastfeeding than mothers
215 included in the analyses. The non-included sample less frequently reported a family history of
216 allergy. The characteristics of the study sample compared by breastfeeding duration
217 categories are available in **Table 1**.

218 ***Longitudinal patterns of infections in infancy***

219 The optimal pattern model for describing diarrhea patterns in infancy was a 4-group model
220 with a square shape for each pattern (**Figure 1A**). The first pattern (9% of children) was
221 characterized by only early events, before age 8 months, and labelled “Only early”. The
222 second pattern (10% of children) was characterized by recurrent events throughout infancy
223 and labelled “High throughout infancy”. The third pattern (43% of children) was
224 characterized by a first event after 4 months and labelled “Lagged occurrence”. The last
225 pattern (38% of children) was characterized by no diarrhea and labelled “Never”.

226 The optimal pattern model for describing otitis patterns in infancy was a 4-group model with
227 a constant shape for the first pattern and a square shape for the 3 other patterns (**Figure 1B**).

228 The first pattern (42% of children) was characterized by no otitis event throughout infancy

229 and labelled “Never”. The second pattern (18% of children) was characterized by a first event
230 after 12 months and labelled “Lagged occurrence”. The third pattern (30% of children) was
231 characterized by increasing events in the first year, with their number remaining moderate up
232 to 2 years, and labelled “Infrequent occurrence”. The last pattern (10% of children) was
233 characterized by increasing events throughout infancy, with a quite high number, and labelled
234 “Increasing throughout infancy”.

235 The optimal pattern model for describing cold/nasopharyngitis patterns in infancy was a 4-
236 group model with a linear shape for the second and fourth patterns and a square shape for the
237 first and third patterns (**Figure 1C**). The first pattern (31% of children) was characterized by a
238 first event after age 4 months and labelled “Lagged occurrence”. The second pattern (49% of
239 children) was characterized by moderate number of events throughout infancy and labelled
240 “Moderate throughout infancy”. The third pattern (16% of children) was characterized by
241 increased number of events throughout infancy and labelled “Increasing throughout infancy”.
242 The last pattern (4% of children) was characterized by a high number of events in early
243 infancy and labelled “High in early frequency”.

244 The optimal pattern model for describing bronchitis/bronchiolitis patterns in infancy was a 4-
245 group model with a cubic shape for the first, second and fourth patterns and a square shape for
246 the third (**Figure 1D**). The first pattern (38% of children) was characterized by no event
247 throughout infancy and labelled “Never”. The second pattern (50% of children) was
248 characterized by increasing events, with their number remaining low, and labelled “Infrequent
249 occurrence”. The third pattern (3% of children) was characterized by peak events at 8 months
250 and labelled “Peak in early infancy”. The last pattern (9% of children) was characterized by
251 increasing events throughout infancy and labelled “Increasing throughout infancy”.

252 *Longitudinal patterns of skin rash and respiratory symptoms in childhood*

253 The optimal pattern model for describing skin rash patterns in childhood was a 5-group model
254 with a square shape for all patterns except the fourth one, which had a cubic shape (**Figure**
255 **2C**). The first pattern (61% of children) was characterized by no skin rashes throughout
256 childhood and labelled “Never”. The second pattern (12% of children) was characterized by a
257 decreasing occurrence of skin rash and labelled “Decreasing throughout childhood”. The third
258 pattern (13% of children) was characterized by an increasing occurrence of events and
259 labelled “Increasing throughout childhood”. The fourth pattern (4% of children) was
260 characterized by a high peak between 2 and 3 years and labelled “Strong peak in early
261 childhood”. The last pattern (10% of children) was characterized by a high occurrence of skin
262 rash throughout childhood and labelled “High throughout childhood”.

263 The optimal pattern model for describing wheezing patterns in childhood was a 5-group
264 model with a square shape for each pattern (**Figure 2A**). The first pattern (13% of children)
265 was characterized by low occurrence of events throughout childhood and labelled “Low
266 occurrence”. The second pattern (11% of children) was characterized by a small peak between
267 12 months and 2 years and labelled “Peak in early childhood”. The third pattern (66% of
268 children) was characterized by no wheezing event throughout childhood and labelled
269 “Never”. The fourth pattern (3% of children) was characterized by decreasing occurrence of
270 wheezing throughout childhood and labelled “Decreasing throughout childhood”. The last
271 pattern (7% of children) was characterized by high occurrence throughout childhood and
272 labelled “High throughout childhood”.

273 The optimal pattern model for describing asthma attack patterns in childhood was a three-
274 group model with a square shape for all patterns (**Figure 2B**). The first pattern (6% of
275 children) was characterized by increasing occurrence of asthma attack throughout childhood
276 and labelled “Increasing throughout childhood”. The second pattern (91% of children) was

277 characterized by no asthma attack and labelled “Never”. The third pattern (3% of children)
278 was characterized by a peak in asthma attacks between 2 and 3 years followed by a relatively
279 steady frequency and labelled “Strong peak in early childhood”.

280 *Breastfeeding and longitudinal patterns of infectious diseases up to 2 years*

281 Both any and predominant breastfeeding were negatively associated with longitudinal patterns
282 of early episodes (<4 months) of diarrhea in the first year of life, whether these episodes
283 persisted or not thereafter. Predominant breastfeeding duration, considered as a continuous
284 variable, was also associated with lower risk of late episodes of diarrhea (Table 2).

285 Any breastfeeding was not associated with otitis events in the first 2 years of life.
286 Nonetheless, predominant breastfeeding duration, considered as a continuous variable, was
287 associated with a lower risk of belonging to the otitis pattern “infrequent occurrence”. The
288 same trend was observed for long duration (≥ 4 months) of predominant breastfeeding (Table
289 2).

290 Breastfeeding was not associated with longitudinal trajectories of colds / nasopharyngitis
291 (Table 3).

292 Predominant breastfeeding and, to a lesser extent, any breastfeeding were both negatively
293 associated with the risk of infrequent occurrence of bronchitis / bronchiolitis in the first 2
294 years of life. Long duration of predominant breastfeeding (≥ 4 months) was also associated
295 with a lower risk of belonging to the trajectory “increasing throughout infancy” of bronchitis /
296 bronchiolitis. The association was not significant when any breastfeeding duration was
297 considered (Table 3).

298 *Breastfeeding and longitudinal patterns of skin rash and respiratory symptoms up to 8* 299 *years*

300 Ever breastfeeding and breastfeeding duration were not related to the longitudinal patterns of
301 skin rash and respiratory symptoms up to 8 years (Tables 4 and 5).

302 **Discussion**

303 In the EDEN mother–child cohort, we confirmed that breastfeeding was related to lower risk
304 of diarrhea events in early infancy and infrequent occurrence of bronchitis/bronchiolitis up to
305 2 years. Moreover, predominant breastfeeding duration was negatively related to the risk of
306 diarrhea events in late infancy, of infrequent otitis occurrence, and of repeated
307 bronchitis/bronchiolitis events throughout infancy. However, we were not able to highlight
308 association between breastfeeding and longitudinal patterns of cold/nasopharyngitis, skin rash
309 or respiratory symptoms.

310 Most of the studies regarding the association between breastfeeding and diarrhea or
311 respiratory infections were conducted in low- and middle-income countries (Horta & Victora,
312 2013), but even in high-income countries, where hygienic conditions do not benefit the
313 development of germs, breastmilk has a protective role. However, the protective role of
314 breastfeeding on gastrointestinal infections may last only while the infant is breastfed and
315 shortly after (Kramer et al., 2003; Quigley, Kelly, & Sacker, 2007). Consistent with these
316 findings, in the EDEN mother–child cohort, ever-breastfed infants were less likely to show
317 longitudinal patterns of diarrhea characterized by increased number of diarrheas in early
318 infancy.

319 Concerning respiratory infections, the last meta-analysis concluded a clear protective effect of
320 breastfeeding (Horta & Victora, 2013). The latter finding was also highlighted in a systematic
321 review of data from high-income countries (Duijts, Ramadhani, & Moll, 2009). In the present
322 study, we did not find such a protective effect on cold/nasopharyngitis. Breastfed children
323 seemed less likely to have infrequent occurrence of bronchitis/bronchiolitis (as compared with
324 never occurrence), whatever the definition used for breastfeeding, whereas only
325 predominantly breastfed infants, especially those breastfed for ≥ 4 months, seemed less likely
326 to have frequent occurrence of bronchitis/bronchiolitis. Our results suggest that breastfeeding

327 may be related to the incidence of respiratory symptoms but also to the reoccurrence of these
328 symptoms throughout infancy. Frequent episodes of bronchiolitis are known to predispose to
329 asthma in the early years of life, so low-frequency bronchitis/bronchiolitis may rely more on
330 infectious origins, whereas high-frequency bronchitis/bronchiolitis may be related to the
331 allergic background of the child. Thus, our results would suggest a protective effect of
332 breastfeeding on respiratory infections. Using other statistical methods, the PARIS cohort
333 highlighted that children who were breastfed for at least 6 months were less likely to have the
334 cough/rhinitis phenotype in the first 4 years of life (Ranciere, Nikasinovic, Bousquet, &
335 Momas, 2013).

336 Concerning ear infections, a recent meta-analysis of studies from the United States and
337 Europe found consistent evidence of a protective effect of breastfeeding on acute otitis media
338 occurrence during the first 2 years of life (Bowatte et al., 2015). In this meta-analysis, the
339 protective effect was clearer when considering exclusive breastfeeding for the first 6 months
340 (odds ratio=0.57 [95% confidence interval 0.44-0.75]) than when considering any
341 breastfeeding for > 3 to 4 months (0.71 [0.42-1.20]). In line with these findings, we did not
342 find any association between any breastfeeding and longitudinal trajectories of otitis but
343 predominant breastfeeding duration was negatively related to the risk of infrequent occurrence
344 of otitis events.

345 The protective effect of breastfeeding on the development of allergic symptoms remains
346 controversial (Victora et al., 2016). Exclusive breastfeeding was found associated with
347 reduced eczema prevalence at age 1 year in the cluster-randomized trial PROBIT (Kramer et
348 al., 2001), but a recent meta-analyses found no evidence of an association with eczema
349 incidence and inconclusive evidence for an association with asthma or wheezing (Kramer &
350 Kakuma, 2012; Lodge et al., 2015). In these meta-analyses, asthma was not considered for
351 children under age 5 in order to avoid misclassification of infants with transient wheezing.

352 Our results agree with these findings despite some noticeable differences in the definition of
353 allergic symptoms. In our study, we used skin rash instead of eczema, which widened the
354 definition of this outcome. Moreover, eczema, wheezing and asthma attacks do not always
355 have an allergic origin. Finally, the EDEN mother–child cohort recorded a wide range of
356 confounding factors such as family history of allergy or age at introduction of solid foods,
357 which did not change the results when adjusted for in the analyses.

358 Beyond nutrients, breast milk transmits immunomodulatory components such as secretory
359 immunoglobulin A, lactoferrin, food antigens or oligosaccharides and microorganisms (Berdi
360 et al., 2018; Hanson et al., 2003; Hoppu, Kalliomaki, Laiho, & Isolauri, 2001; Petherick,
361 2010). These components may influence gut microbiota as human milk oligosaccharides are
362 substrates for the development of certain beneficial bacterial strains (Coppa, Bruni, Morelli,
363 Soldi, & Gabrielli, 2004) and microorganisms may colonize the infant's digestive tract and
364 prevent the development of other potentially harmful strains (Petherick, 2010).

365 To our knowledge, few studies have used group-based trajectory modeling to assess infection
366 and allergic development. The method allows for longitudinal classification of infants and
367 discrimination between transient and regular outbreaks, which can reflect the infant's
368 susceptibility to infections and allergic profile. As any statistical method, the GBTM method
369 is not perfect. It is not always easy to find the optimal number of groups or the right shape for
370 each pattern. Criteria such as BIC, averagePP or OCC are useful objective tools for decision
371 making regarding the choice of number of groups but the consistency of these groups with
372 real life must not be neglected. Nonetheless, when assessing the links between breastfeeding
373 and these patterns, the method brings additional information such as whether a potential
374 association is found only when the infant is still breastfed or even after breastfeeding
375 cessation or whether breastfeeding is associated with the temporal evolution of a symptom.
376 Comparison of the same patterns from larger and foreign cohorts would give good

377 information on the development of these outcomes and may lead to targeted interventions to
378 prevent them.

379 The EDEN mother–child cohort is a French ongoing regional observational study. Due to the
380 sample selection and attrition issues, these results cannot be generalized to the whole
381 population. In high-income countries, wealthy families are more likely to breastfed their
382 infants and these infants are at lower risk of infections, which can lead to a probable
383 overestimation of the associations between breastfeeding and lower risk of infection.
384 Therefore, further studies need to be conducted, especially in disadvantaged families.
385 However, the insights and long-term follow-up of our results represent a major asset. Recent
386 data from a French nationwide birth cohort reported 70% breastfeeding initiation and 22%
387 breastfeeding rates at 4 months (Wagner et al., 2015), whereas in the EDEN mother–child
388 cohort, 74% of children were ever breastfed and 36% were breastfed for at least 4 months.
389 Breastfeeding rates in the EDEN cohort are higher than national ones, but still below
390 guidelines.

391 **Conclusion**

392 Despite a context of low rate and duration of breastfeeding and high hygienic conditions, we
393 found, using a longitudinal approach, a beneficial association between breastfeeding and
394 diarrhea, bronchitis/bronchiolitis and, to a lesser extent, otitis during infancy. The use of
395 longitudinal patterns of infections allowed us to confirm that the potential protective effect of
396 breastfeeding on diarrhea events seems to be maximized when breastfeeding is still ongoing.
397 However, we were not able to highlight any association between breastfeeding and skin rash
398 or respiratory symptoms. These results and particularly the use of group-based trajectory
399 modeling need to be replicated in larger and representative cohorts. Nonetheless, the
400 promotion and facilitation of breastfeeding initiation and duration are part of prevention of the

401 occurrence of infections and hence reduce their economic cost due to health care system
402 usage (hospitalization, medication etc.) and parental leave from work.

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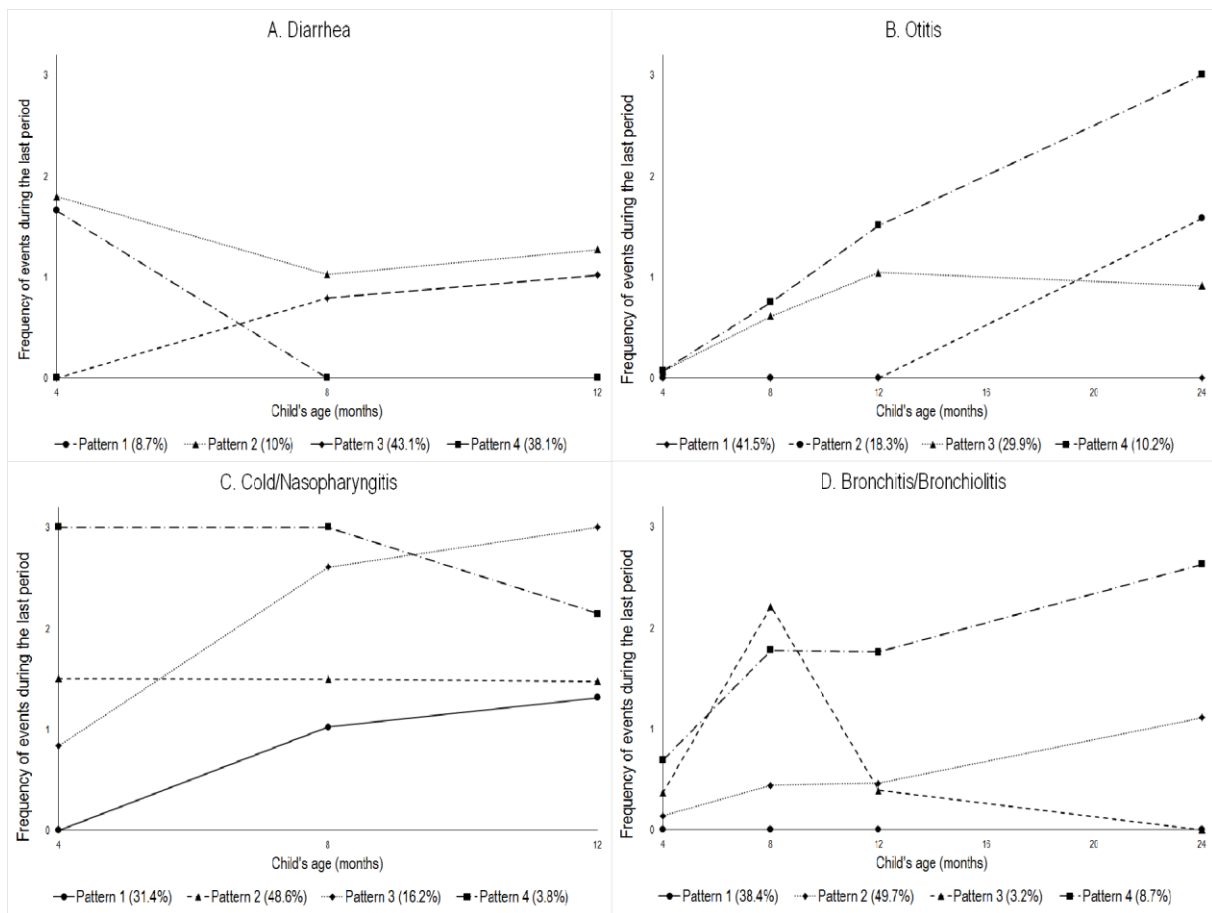
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479 *countries*. Retrieved from Geneva:
- 480

481 **Table 1:** Characteristics of the study sample according to any breastfeeding duration (n=1,603 children)

	<i>Any breastfeeding duration</i>		
	<1 month	1 to 4 months	≥4 months
N	523	510	570
Recruitment in Poitiers	63.7% (333)	42.2% (215)	38.8% (221)
Familial history of allergy	49.7% (260)	52.7% (269)	54.7% (312)
Primiparous mother	44.2% (231)	50.2% (256)	43.9% (250)
Maternal smoking during pregnancy	31.5% (165)	25.1% (128)	15.1% (86)
Maternal master's degree	22.0% (115)	33.5% (171)	47.9% (273)
Maternal age at birth (years)	29.4 (± 4.9)	29.3 (± 4.7)	30.5 (± 4.6)
Family monthly income			
≤€ 1,500	17.0% (89)	11.2% (57)	12.3% (70)
€ 1,501 - 2,300	37.3% (195)	29.8% (152)	22.8% (130)
€ 2,301 - 3,000	25.8% (135)	28.4% (145)	28.4% (162)
€ 3,001 - 3,800	13.0% (68)	17.8% (91)	19.6% (112)
€ 3,801	6.9% (36)	12.7% (65)	16.8% (96)
Boy	53.2% (278)	54.5% (278)	48.9% (279)
Preterm birth	5.2% (27)	6.9% (35)	4.0% (23)
C-section delivery	16.6% (87)	16.5% (84)	14.7% (84)
Age at first attendance to collective care arrangement			
Before 4 months	16.4% (86)	21.4% (109)	15.1% (86)
Between 4 and 8 months	6.9% (36)	11.6% (59)	17.5% (100)
Between 8 and 12 years	2.1% (11)	4.1% (21)	5.3% (30)
Never	74.6% (390)	62.9% (321)	62.1% (354)
Age at solid food introduction	3.9 (± 1.7)	4.2 (± 1.6)	5.0 (± 1.4)

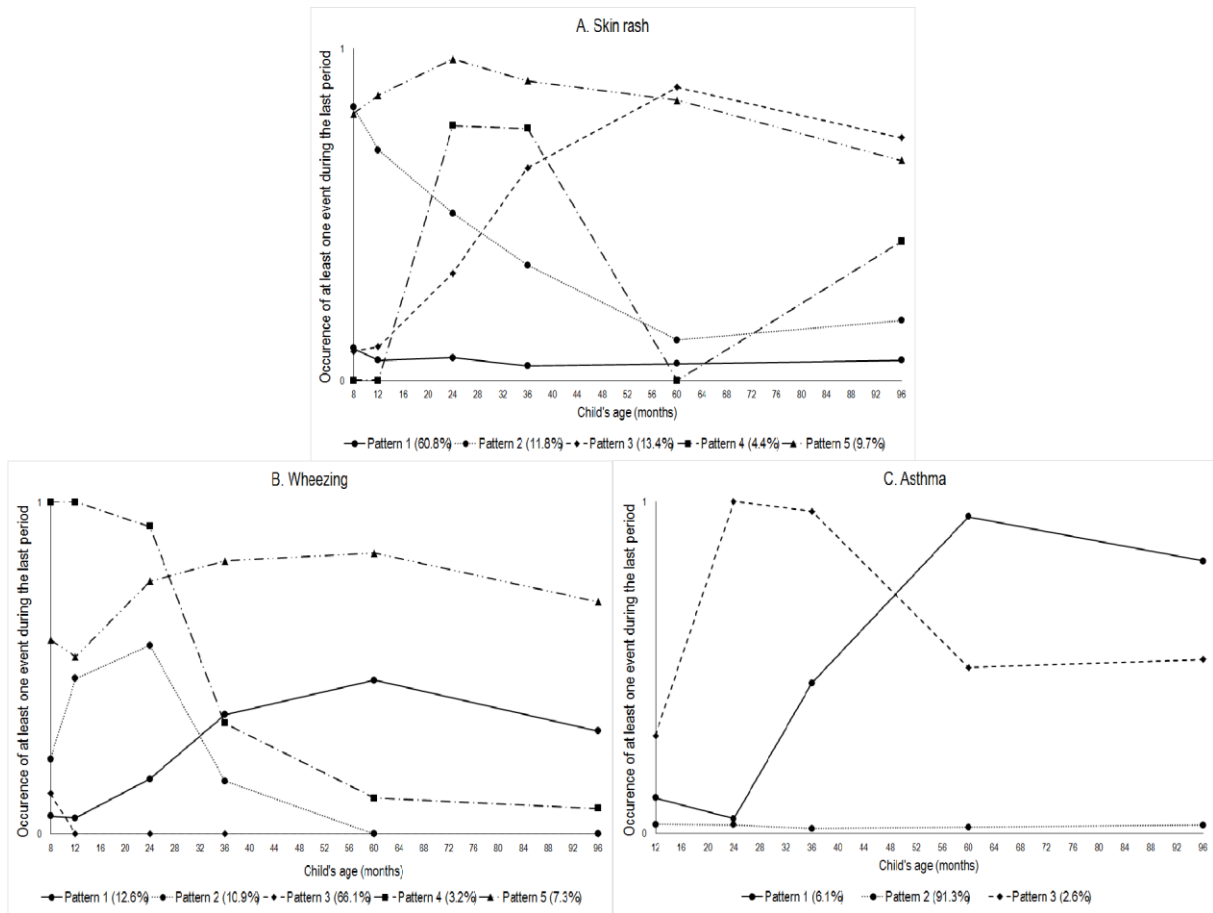
% (n) or mean (± sd)

482 **Figure 1:** Longitudinal patterns of diarrhea, otitis, cold/nasopharyngitis and
 483 bronchitis/bronchiolitis up to 2 years (n = 1,603)



484
 485 Pattern legend. A-Diarrhea: 1) “Only early”, 2) “High throughout infancy”, 3) “Lagged
 486 occurrence”, 4) “Never”; B-Otitis: 1) “Never”, 2) “Lagged occurrence”, 3) “Infrequent
 487 occurrence”, 4) “Increasing throughout infancy”; C-Cold/nasopharyngitis: 1) “Lagged
 488 occurrence”, 2) “Moderate throughout infancy”, 3) “Increasing throughout infancy”, 4) “High
 489 throughout infancy”; D-Bronchitis/bronchiolitis: 1) “Never”, 2) “Infrequent occurrence”, 3)
 490 “Peak in early infancy”, 4) “Increasing throughout infancy”.

491 **Figure 2:** Longitudinal patterns of skin rash, wheezing and asthma attack up to 8 years (n =
 492 1,377)



493
 494 Pattern legend. A-Skin rash: 1) “Never”. 2) “Decreasing throughout childhood”, 3)
 495 “Increasing throughout childhood”, 4) “Strong peak in early childhood”, 5) “High throughout
 496 childhood”; B-Wheezing: 1) “Low occurrence”, 2) “Peak in early childhood”, 3) “Never”, 4)
 497 “Decreasing throughout childhood”, 5) “High throughout childhood”; C-Asthma attack: 1)
 498 “Increasing throughout childhood”, 2) “Never”, 3) “Strong peak in early childhood”.

499 **Table 2.** Adjusted associations between breastfeeding status and longitudinal patterns of diarrhea up to 1 year and otitis up to 2 years (n = 1,603)

	Diarrhea (ref: never)				Otitis (ref: never)			
	Only early	High throughout infancy	Lagged occurrence	<i>p</i>	Lagged occurrence	Infrequent occurrence	Increasing throughout infancy	<i>p</i>
Any breastfeeding				<1.10-4				0.3
Never breastfed	1 [Ref]	1 [Ref]	1 [Ref]		1 [Ref]	1 [Ref]	1 [Ref]	
Ever breastfed	0.51 [0.33 ; 0.78]	0.41 [0.27 ; 0.60]	1.09 [0.82 ; 1.43]		0.81 [0.58 ; 1.15]	0.87 [0.65 ; 1.16]	0.68 [0.45 ; 1.03]	
Any breastfeeding duration (months)				<1.10-4				0.2
0.86 [0.80 ; 0.92]	0.85 [0.80 ; 0.91]	0.99 [0.96 ; 1.02]		1.00 [0.96 ; 1.04]	0.97 [0.94 ; 1.01]	0.96 [0.91 ; 1.01]		
Any breastfeeding duration < 1 month				<1.10-4				0.5
1 [Ref]	1 [Ref]	1 [Ref]		1 [Ref]	1 [Ref]	1 [Ref]		
1 to < 4 months	0.52 [0.33 ; 0.81]	0.42 [0.27 ; 0.65]	0.90 [0.67 ; 1.20]		0.93 [0.65 ; 1.34]	0.96 [0.71 ; 1.30]	0.77 [0.49 ; 1.20]	
≥ 4 months	0.27 [0.16 ; 0.46]	0.28 [0.17 ; 0.45]	1.02 [0.76 ; 1.37]		0.88 [0.61 ; 1.27]	0.76 [0.55 ; 1.04]	0.69 [0.43 ; 1.09]	
Predominant breastfeeding				< 1.10-4				0.2
Never breastfed	1 [Ref]	1 [Ref]	1 [Ref]		1 [Ref]	1 [Ref]	1 [Ref]	
Ever breastfed	0.48 [0.33 ; 0.72]	0.41 [0.28 ; 0.59]	0.95 [0.74 ; 1.21]		0.81 [0.59 ; 1.10]	0.87 [0.67 ; 1.14]	0.70 [0.48 ; 1.02]	
Predominant breastfeeding duration (months)				<1.10-4				0.03
0.85 [0.77 ; 0.93]	0.79 [0.72 ; 0.88]	0.95 [0.91 ; 0.99]		0.97 [0.92 ; 1.02]	0.93 [0.88 ; 0.97]	0.96 [0.89 ; 1.03]		
Predominant breastfeeding duration < 1 month				< 1.10-4				0.08
1 [Ref]	1 [Ref]	1 [Ref]		1 [Ref]	1 [Ref]	1 [Ref]		
1 to < 4 months	0.42 [0.27 ; 0.65]	0.43 [0.28 ; 0.64]	0.96 [0.75 ; 1.23]		0.87 [0.63 ; 1.19]	0.85 [0.65 ; 1.11]	0.75 [0.50 ; 1.11]	
≥ 4 months	0.35 [0.19 ; 0.65]	0.25 [0.13 ; 0.47]	0.75 [0.54 ; 1.04]		0.72 [0.47 ; 1.09]	0.54 [0.37 ; 0.80]	0.70 [0.42 ; 1.19]	

500 Data are multinomial OR [95% CI], adjusted for center, family history of allergy, parity, smoking status during pregnancy, maternal education
 501 level, maternal age at birth, family monthly income, sex, gestational age, caesarean section, age at first attendance to collective care arrangement,
 502 age at introduction of solid food. Separate models were conducted for each breastfeeding exposure and for each outcome, diarrhea or otitis.

503 **Table 3.** Adjusted associations between breastfeeding status and longitudinal patterns of respiratory infections in infancy (n = 1,603)

	Cold/nasopharyngitis (ref: moderate throughout infancy)			<i>p</i>	Bronchitis/bronchiolitis (ref: never)			<i>p</i>
	Lagged occurrence	Increasing throughout infancy	High in early infancy		Infrequent occurrence	Peak in early infancy	Increasing throughout infancy	
Any breastfeeding				<i>0.3</i>				<i>0.1</i>
Never breastfed	1 [Ref]	1 [Ref]	1 [Ref]		1 [Ref]	1 [Ref]	1 [Ref]	
Ever breastfed	1.02 [0.77 ; 1.35]	1.34 [0.94 ; 1.93]	1.36 [0.71 ; 2.59]		0.75 [0.58 ; 0.98]	0.53 [0.27 ; 1.06]	0.82 [0.52 ; 1.30]	
Any breastfeeding duration (months)				<i>0.7</i>				<i>0.06</i>
Any breastfeeding duration	1.00 [0.97 ; 1.03]	0.98 [0.94 ; 1.02]	0.98 [0.90 ; 1.06]		0.96 [0.93 ; 0.99]	0.95 [0.87 ; 1.04]	0.95 [0.90 ; 1.01]	
Any breastfeeding duration < 1 month				<i>0.9</i>				<i>0.2</i>
< 1 month	1 [Ref]	1 [Ref]	1 [Ref]		1 [Ref]	1 [Ref]	1 [Ref]	
1 to < 4 months	1.14 [0.85 ; 1.53]	1.02 [0.70 ; 1.47]	1.21 [0.63 ; 2.32]		0.71 [0.54 ; 0.94]	0.83 [0.40 ; 1.73]	0.81 [0.50 ; 1.29]	
≥ 4 months	1.15 [0.85 ; 1.55]	1.04 [0.71 ; 1.52]	0.81 [0.39 ; 1.68]		0.75 [0.56 ; 0.99]	0.59 [0.27 ; 1.31]	0.64 [0.38 ; 1.07]	
Predominant breastfeeding				<i>0.8</i>				<i>0.04</i>
Never breastfed	1 [Ref]	1 [Ref]	1 [Ref]		1 [Ref]	1 [Ref]	1 [Ref]	
Ever breastfed	1.13 [0.88 ; 1.46]	1.01 [0.74 ; 1.39]	1.12 [0.62 ; 2.02]		0.74 [0.58 ; 0.94]	0.57 [0.30 ; 1.07]	0.69 [0.45 ; 1.04]	
Predominant breastfeeding duration (months)				<i>0.1</i>				<i>0.003</i>
Predominant breastfeeding duration	1.03 [0.99 ; 1.08]	0.95 [0.89 ; 1.01]	1.01 [0.90 ; 1.13]		0.93 [0.90 ; 0.97]	0.94 [0.84 ; 1.06]	0.88 [0.80 ; 0.96]	
Predominant breastfeeding duration < 1 month				<i>0.6</i>				<i>0.07</i>
< 1 month	1 [Ref]	1 [Ref]	1 [Ref]		1 [Ref]	1 [Ref]	1 [Ref]	
1 to < 4 months	1.12 [0.87 ; 1.46]	0.80 [0.58 ; 1.11]	1.04 [0.57 ; 1.89]		0.89 [0.70 ; 1.14]	0.98 [0.51 ; 1.88]	0.73 [0.48 ; 1.12]	
≥ 4 months	1.11 [0.79 ; 1.57]	0.75 [0.48 ; 1.18]	1.11 [0.48 ; 2.56]		0.64 [0.46 ; 0.88]	0.57 [0.23 ; 1.43]	0.44 [0.23 ; 0.83]	

504 Data are multinomial OR [95% CI], adjusted for center, family history of allergy, parity, smoking status during pregnancy, maternal education
505 level, maternal age at birth, family monthly income, sex, gestational age, caesarean section, age at first attendance to collective care arrangement,
506 age at introduction of solid food. Separate models were conducted for each breastfeeding exposure and for each outcome, cold/nasopharyngitis or
507 bronchitis/bronchiolitis.

508 **Table 4.** Adjusted associations between breastfeeding status and longitudinal patterns of skin rash in childhood (n = 1,377)

	Skin rash				<i>p</i>
	(ref: never)				
	Decreasing throughout childhood	Increasing throughout childhood	Strong peak in early childhood	High throughout childhood	
Any breastfeeding					<i>0.5</i>
Never breastfed	1 [Ref]	1 [Ref]	1 [Ref]	1 [Ref]	
Ever breastfed	0.81 [0.54 ; 1.20]	0.96 [0.65 ; 1.42]	1.70 [0.81 ; 3.55]	1.04 [0.66 ; 1.64]	
Any breastfeeding duration (months)	1.00 [0.95 ; 1.05]	0.99 [0.94 ; 1.04]	1.03 [0.96 ; 1.11]	0.97 [0.91 ; 1.02]	<i>0.7</i>
Any breastfeeding duration					<i>0.5</i>
< 1 month	1 [Ref]	1 [Ref]	1 [Ref]	1 [Ref]	
1 to < 4 months	0.99 [0.65 ; 1.53]	0.96 [0.63 ; 1.47]	2.22 [1.06 ; 4.65]	1.24 [0.78 ; 1.98]	
≥ 4 months	0.95 [0.61 ; 1.49]	0.98 [0.64 ; 1.50]	1.76 [0.81 ; 3.80]	0.82 [0.49 ; 1.36]	
Predominant breastfeeding					<i>0.8</i>
Never breastfed	1 [Ref]	1 [Ref]	1 [Ref]	1 [Ref]	
Ever breastfed	0.89 [0.62 ; 1.29]	0.91 [0.64 ; 1.30]	1.37 [0.73 ; 2.58]	1.07 [0.70 ; 1.63]	
Predominant breastfeeding duration (months)	0.96 [0.89 ; 1.03]	1.00 [0.94 ; 1.07]	0.85 [0.71 ; 1.01]	0.99 [0.91 ; 1.07]	<i>0.3</i>
Predominant breastfeeding duration					<i>0.8</i>
< 1 month	1 [Ref]	1 [Ref]	1 [Ref]	1 [Ref]	
1 to < 4 months	1.03 [0.70 ; 1.51]	0.89 [0.61 ; 1.28]	1.31 [0.71 ; 2.41]	1.21 [0.80 ; 1.84]	
≥ 4 months	1.13 [0.66 ; 1.92]	1.23 [0.77 ; 1.99]	1.38 [0.63 ; 3.01]	0.91 [0.50 ; 1.66]	

509 Data are multinomial OR [95% CI], adjusted for center, family history of allergy, parity, smoking status during pregnancy, maternal education
 510 level, maternal age at birth, family monthly income, sex, gestational age, caesarean section, age at first attendance to collective care arrangement,
 511 age at introduction of solid food. . Separate models were conducted for each breastfeeding exposure.

512 **Table 5.** Adjusted associations between breastfeeding status and longitudinal patterns of respiratory allergic symptoms in childhood (n = 1,377)

	Wheezing (ref: never)				<i>p</i>	Asthma attack (ref: never)		<i>p</i>
	Low occurrence	Peak in early childhood	Decreasing throughout childhood	High throughout childhood		Increasing throughout childhood	Strong peak in early childhood	
Any breastfeeding					<i>0.9</i>			<i>0.4</i>
Never breastfed	1 [Ref]	1 [Ref]	1 [Ref]	1 [Ref]		1 [Ref]	1 [Ref]	
Ever breastfed	1.04 [0.70 ; 1.55]	0.94 [0.61 ; 1.44]	0.74 [0.36 ; 1.52]	0.94 [0.57 ; 1.55]		1.30 [0.76 ; 2.24]	0.69 [0.32 ; 1.47]	
Any breastfeeding duration (months)					<i>0.3</i>			<i>1</i>
	0.97 [0.92 ; 1.02]	1.00 [0.95 ; 1.05]	0.91 [0.82 ; 1.02]	1.01 [0.95 ; 1.08]		1.00 [0.94 ; 1.07]	1.01 [0.91 ; 1.12]	<i>1</i>
Any breastfeeding duration					<i>0.6</i>			<i>0.7</i>
< 1 month	1 [Ref]	1 [Ref]	1 [Ref]	1 [Ref]		1 [Ref]	1 [Ref]	
1 to < 4 months	1.27 [0.84 ; 1.93]	0.89 [0.57 ; 1.41]	0.70 [0.32 ; 1.50]	0.77 [0.44 ; 1.34]		1.01 [0.56 ; 1.82]	0.65 [0.27 ; 1.56]	
≥ 4 months	0.93 [0.60 ; 1.46]	0.95 [0.60 ; 1.51]	0.56 [0.24 ; 1.27]	1.03 [0.60 ; 1.77]		1.34 [0.75 ; 2.40]	1.04 [0.44 ; 2.46]	
Predominant breastfeeding								<i>1</i>
Never breastfed	1 [Ref]	1 [Ref]	1 [Ref]	1 [Ref]	<i>0.4</i>	1 [Ref]	1 [Ref]	
Ever breastfed	1.01 [0.70 ; 1.46]	0.81 [0.55 ; 1.20]	0.56 [0.29 ; 1.09]	0.96 [0.60 ; 1.53]		1.05 [0.64 ; 1.71]	1.03 [0.50 ; 2.14]	
Predominant breastfeeding duration (months)					<i>0.6</i>			<i>0.6</i>
	1.02 [0.96 ; 1.09]	0.99 [0.93 ; 1.06]	1.04 [0.95 ; 1.15]	0.96 [0.89 ; 1.04]		1.01 [0.92 ; 1.10]	1.08 [0.94 ; 1.24]	<i>0.6</i>
Predominant breastfeeding duration					<i>0.2</i>			<i>1</i>
< 1 month	1 [Ref]	1 [Ref]	1 [Ref]	1 [Ref]		1 [Ref]	1 [Ref]	
1 to < 4 months	1.23 [0.85 ; 1.77]	0.89 [0.60 ; 1.32]	0.55 [0.27 ; 1.10]	0.98 [0.62 ; 1.56]		1.03 [0.62 ; 1.72]	0.75 [0.35 ; 1.62]	
≥ 4 months	0.71 [0.41 ; 1.22]	0.8 [0.47 ; 1.35]	0.40 [0.14 ; 1.16]	0.60 [0.30 ; 1.22]		0.97 [0.48 ; 1.97]	0.97 [0.33 ; 2.89]	

513 Data are multinomial OR [95% CI], adjusted for center, family history of allergy, parity, smoking status during pregnancy, maternal education
514 level, maternal age at birth, family monthly income, sex, gestational age, caesarean section, age at first attendance to collective care arrangement,
515 age at introduction of solid food. Separate models were conducted for each breastfeeding exposure and for each outcome, wheezing or asthma
516 attack.

517 **SUPPORTING INFORMATION**

518 **Supplementary table 1:** Comparison of included and excluded families (Chi2 and Student t-
519 tests)

	Selected	Excluded	p
Recruitment in Poitiers	48.0% (769)	49.9% (199)	0.500
Familial history of allergy	52.5% (841)	36.8% (147)	0.000
Primiparous mother	46.0% (737)	37.0% (111)	0.004
Maternal smoking during pregnancy	23.6% (379)	43.0% (105)	0.000
Maternal master's degree	34.9% (559)	15.6% (48)	0.000
Maternal age at birth (years)	29.8 (\pm 4.8)	28.0 (\pm 5.2)	0.000
Family monthly income			0.000
\leq € 1,500	13.5% (216)	35.8% (111)	
€ 1,501 – 2,300	29.8% (477)	29.4% (91)	
€ 2,301 – 3,000	27.6% (442)	19.0% (59)	
€ 3,001 – 3,800	16.9% (271)	7.4% (23)	
€ 3,801	12.3% (197)	8.4% (26)	
Boy	52.1% (835)	55.0% (165)	0.350
Preterm birth	5.3% (85)	8.3% (25)	0.040
C-section delivery	15.9% (255)	14.9% (44)	0.650
Age at first attendance to collective care arrangement			0.001
Before 4 months	17.5% (281)	7.6% (9)	
Between 4 and 8 months	12.2% (195)	6.8% (8)	
Between 8 and 12 years	3.9% (62)	1.7% (2)	
Never	66.4% (1065)	83.9% (99)	
Age at solid food introduction	4.4 (\pm 1.6)	4.6 (\pm 1.9)	0.13

% (n) or mean (\pm sd)

520

521 **Supplementary table 2:** Model criteria for longitudinal patterns of infection

	<i>Diarrhea</i>	<i>Otitis</i>	<i>Cold/ nasopharyngitis</i>	<i>Bronchitis/ bronchiolitis</i>
Pattern model criteria				
BIC	-4217.93	-4548.05	-5091.26	-6830.17
Estimated prevalence				
First group	0.108	0.282	0.245	0.293
Second group	0.174	0.214	0.584	0.510
Third group	0.487	0.404	0.142	0.091
Fourth group	0.231	0.101	0.029	0.107
Actual prevalence				
First group	0.087	0.415	0.314	0.384
Second group	0.1	0.183	0.486	0.497
Third group	0.431	0.299	0.162	0.032
Fourth group	0.381	0.102	0.038	0.087
Average PP				
First group	0.743	0.679	0.712	0.717
Second group	0.986	0.687	0.932	0.797
Third group	0.828	0.943	0.687	0.569
Fourth group	0.541	0.777	0.697	0.825
OCC				
First group	23.878	5.386	7.618	6.113
Second group	334.333	8.062	9.763	3.772
Third group	5.071	24.406	13.262	13.187
Fourth group	3.924	31.014	77.021	39.344

522 BIC, Bayesian Information Criteria; PP, Posterior Probability; OCC, Odds of Correct
523 Classification

524

525 **Supplementary table 3:** Model criteria for longitudinal patterns of allergic symptoms

	<i>Wheezing</i>	<i>Skin rash</i>	<i>Asthma attack</i>
Pattern model criteria			
BIC	-2911.67	-4055.77	-1146.49
Estimated prevalence			
First group	0.188	0.563	0.067
Second group	0.212	0.137	0.904
Third group	0.488	0.141	0.029
Fourth group	0.035	0.062	
Fifth group	0.077	0.097	
Actual prevalence			
First group	0.126	0.608	0.061
Second group	0.109	0.118	0.913
Third group	0.661	0.134	0.026
Fourth group	0.032	0.044	
Fifth group	0.073	0.097	
Average PP			
First group	0.815	0.868	0.860
Second group	0.727	0.703	0.985
Third group	0.738	0.744	0.916
Fourth group	0.773	0.561	
Fifth group	0.812	0.812	
OCC			
First group	19.028	5.104	85.542
Second group	9.898	14.910	6.973
Third group	2.955	17.705	365.122
Fourth group	93.889	19.333	
Fifth group	51.774	40.208	

526 BIC, Bayesian Information Criteria; PP, Posterior Probability; OCC, Odds of Correct
527 Classification

528 **Supplementary table 4:** Non-adjusted association between breastfeeding, any or predominant, and diarrhea and otitis in infancy (n = 1,603, chi-
 529 square test)

	Diarrhea				<i>p</i>	Otitis				<i>p</i>
	Never	Only early	High throughout infancy	Lagged occurrence		Never	Lagged occurrence	Infrequent occurrence	Increasing throughout infancy	
Any breastfeeding					<10-4					0.5
Never breastfed	23% (139)	39% (54)	43% (69)	22% (149)		24% (161)	25% (73)	27% (129)	29% (48)	
Breastfed	77% (472)	61% (86)	57% (92)	78% (542)		76% (504)	75% (221)	73% (351)	71% (116)	
Any breastfeeding duration					<10-4					0.7
< 1 month	28% (171)	50% (70)	52% (84)	29% (198)		32% (213)	30% (89)	34% (163)	35% (58)	
1 to < 4 months	34% (205)	31% (43)	27% (44)	32% (218)		31% (207)	32% (93)	34% (161)	30% (49)	
≥ 4 months	38% (235)	19% (27)	21% (33)	40% (275)		37% (245)	38% (112)	33% (156)	35% (57)	
Predominant breastfeeding					<10-4					0.7
Never breastfed	30% (181)	47% (66)	52% (83)	30% (209)		32% (215)	33% (98)	34% (165)	37% (61)	
Ever breastfed	70% (429)	53% (74)	48% (78)	70% (482)		68% (449)	67% (196)	66% (315)	63% (103)	
Predominant breastfeeding duration					<10-4					0.2
< 1 month	40% (242)	61% (86)	64% (103)	42% (288)		43% (285)	44% (129)	48% (229)	46% (76)	
1 to < 4 months	40% (244)	27% (38)	28% (45)	42% (289)		38% (252)	39% (115)	40% (190)	36% (59)	
≥ 4 months	20% (124)	12% (16)	8% (13)	16% (114)		19% (127)	17% (50)	12% (61)	18% (29)	

% (n)

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533 **Supplementary table 5:** Non-adjusted association between breastfeeding, any or predominant, and cold/nasopharyngitis and
 534 bronchitis/bronchiolitis in infancy (n = 1,603, chi-square test)

	Cold/nasopharyngitis				<i>p</i>	Bronchitis/bronchiolitis				<i>p</i>
	Lagged occurrence	Moderate throughout infancy	Increasing throughout infancy	High in early infancy		Never	Infrequent occurrence	Peak in early infancy	Increasing throughout infancy	
Any breastfeeding					<i>0.1</i>					<i>0.1</i>
Never breastfed	23.7% (119)	28.2% (220)	21.5% (56)	26.2% (16)		22% (138)	28% (221)	29% (15)	27% (37)	
Breastfed	76.3% (384)	71.8% (559)	78.5% (204)	73.8% (45)		78% (478)	72% (575)	71% (37)	73% (102)	
Any breastfeeding duration					<i>0.2</i>					<i>0.1</i>
< 1 month	28% (144)	35% (275)	32% (82)	36% (22)		29% (176)	35% (282)	31% (16)	35% (49)	
1 to < 4 months	32% (163)	31% (242)	32% (83)	36% (22)		33% (203)	30% (239)	37% (19)	35% (49)	
≥ 4 months	39% (196)	34% (262)	37% (95)	28% (17)		38% (237)	35% (275)	33% (17)	30% (41)	
Predominant breastfeeding					<i>0.3</i>					<i>0.03</i>
Never breastfed	30% (153)	36% (278)	34% (87)	34% (21)		29% (180)	36% (286)	38.5% (20)	38.1% (53)	
Ever breastfed	70% (350)	64% (501)	66% (172)	66% (40)		71% (436)	64% (509)	61.5% (32)	61.9% (86)	
Predominant breastfeeding duration					<i>0.6</i>					<i>0.04</i>
< 1 month	41% (208)	46% (358)	49% (126)	44% (27)		41% (254)	46% (370)	42% (22)	52% (73)	
1 to < 4 months	41% (203)	38% (295)	36% (94)	39% (24)		39% (237)	39% (307)	42% (22)	36% (50)	
≥ 4 months	18% (92)	16% (126)	15% (39)	16% (10)		20% (125)	15% (118)	16% (8)	12% (16)	

% (n)

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537 **Supplementary table 6:** Non-adjusted association between breastfeeding, any or predominant, and skin rash in infancy (n = 1,377, chi-square
 538 test)

	Skin rash					<i>p</i>
	Never	Decreasing throughout childhood	Increasing throughout childhood	Strong peak in early childhood	High throughout childhood	
Any breastfeeding						
Never breastfed	24% (205)	32% (52)	27% (49)	16% (10)	26% (34)	<i>0,1</i>
Breastfed	76% (632)	68% (110)	73% (135)	84% (51)	74% (99)	
Any breastfeeding duration						
< 1 month	32% (268)	36% (59)	33% (61)	20% (12)	34% (45)	<i>0,3</i>
1 to < 4 months	31% (258)	31% (50)	29% (53)	39% (24)	36% (48)	
≥ 4 months	37% (311)	33% (53)	38% (70)	41% (25)	30% (40)	
Predominant breastfeeding						<i>0,4</i>
Never breastfed	33% (274)	38% (61)	35% (64)	25% (15)	32% (43)	
Ever breastfed	67% (562)	62% (101)	65% (120)	75% (46)	68% (90)	
Predominant breastfeeding duration						<i>0,8</i>
< 1 month	45% (374)	46% (75)	45% (82)	36% (22)	44% (58)	
1 to < 4 months	39% (326)	38% (62)	36% (66)	42% (26)	42% (56)	
≥ 4 months	16% (136)	15% (25)	19% (36)	21% (13)	14% (19)	
% (n)						

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540 **Supplementary table 7:** Non-adjusted association between breastfeeding, any or predominant, and wheezing and asthma in infancy (n = 1,377,
 541 chi-square test)

	Wheezing					<i>p</i>	Asthma attack			<i>p</i>
	Never	Low occurrence	Peak in early childhood	Decreasing throughout childhood	High throughout childhood		Never	Increasing throughout childhood	Strong peak in early childhood	
Any breastfeeding status						<i>0,9</i>				<i>0,3</i>
Never breastfed	25% (227)	26% (45)	25% (37)	30% (13)	28% (28)		25% (315)	26% (22)	36% (13)	
Breastfed	75% (683)	74% (128)	75% (113)	70% (31)	72% (72)		75% (942)	74% (62)	64% (23)	
Any breastfeeding duration						<i>0,8</i>				<i>0,9</i>
< 1 month	32% (291)	31% (54)	32% (48)	39% (17)	35% (35)		32% (401)	35% (29)	42% (15)	
1 to < 4 months	31% (284)	36% (63)	30% (45)	32% (14)	27% (27)		32% (400)	29% (24)	25% (9)	
≥ 4 months	37% (335)	32% (56)	38% (57)	30% (13)	28% (38)		36% (456)	37% (31)	33% (12)	
Predominant breastfeeding						<i>0,7</i>				<i>0,7</i>
Never breastfed	32% (293)	34% (58)	36% (54)	41% (18)	34% (34)		33% (413)	37% (31)	36% (13)	
Ever breastfed	68% (616)	66% (115)	64% (96)	59% (26)	66% (66)		67% (843)	63% (53)	64% (23)	
Predominant breastfeeding duration						<i>0,4</i>				<i>0,8</i>
< 1 month	44% (397)	43% (74)	46% (69)	55% (24)	47% (47)		44% (552)	48% (40)	53% (19)	
1 to < 4 months	38% (348)	4% (77)	37% (55)	34% (15)	41% (41)		39% (493)	37% (31)	33% (12)	
≥ 4 months	18% (164)	13% (22)	17% (26)	11% (5)	12% (12)		17% (211)	15% (13)	14% (5)	

% (n)

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